

REMARKS

Applicants have hereinabove canceled claims 1-8 and 12, and have amended pending claims 9-11 and 13-17 to more clearly describe and distinctly claim the subject matter of the instant invention. Support for amending the claims to recite a dry analytical element having at least one layer comprising gelatin may be found in the specification at, inter alia, page 2, beginning at line 19, page 3, lines 12-16, page 9, lines 1-7, and Table 1a, page 11. The remaining amendments to the claims introduce only minor format and grammatical changes. Accordingly, the amendments to the claims raise no issue of new matter.

In view of the amendments to the claims and the arguments put forth herein, applicants maintain that the Examiner's rejections have been overcome and respectfully request that they be withdrawn.

The Instant Invention

The invention as claimed provides a dry analytical element for determining acetominophen in an aqueous fluid using an arylacylamidase enzyme reaction. The element employs, in relevant part, a ferricyanide oxidizing agent, a water-soluble coupling agent, a gelatin component, and a buffered pH of from about 6.5 to 8.5.

The art teaches chemical problems which at the time of this invention would have been expected to prevent the success of the instant analytical element. These problems include gelatin hardening at the alkaline pH thought to be required for oxidative dye formation, and the undesirability of using ferricyanide as an

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oxidizing agent. The instant analytical element surprisingly overcomes these problems.

Rejection Under 35 U.S.C. 102(b)

The Examiner rejected claims 1-7, 9-12, 14, and 17 under 35 U.S.C. 102(b) as allegedly anticipated by Arter. Claims 1-7 and 12 have been canceled hereinabove.

In response, applicants respectfully traverse the Examiner's rejection. Claims 9-11, 14 and 17 provide an analytical element comprising, inter alia, a ferricyanide salt as an oxidizing agent and a water-soluble coupler. Arter fails to teach either of these elements. Thus, Arter does not anticipate any of claims 9-11, 14 and 17 under 35 U.S.C. 102(b) as alleged.

Rejection Under 35 U.S.C. 103

The Examiner rejected claims 8, 13, 15, and 16 under 35 U.S.C. 103 as allegedly unpatentable over Arter and further in view of Kawaguchi. Claim 8 has been canceled hereinabove.

In response, applicants respectfully traverse the Examiner's rejection, and maintain that the Examiner has not established a *prima facie* case of obviousness. Claims 8, 13, 15, and 16 provide an analytical element comprising, inter alia, a ferricyanide salt as an oxidizing agent, a water-soluble coupler, and maleimide which acts to protect the analytical element against interfering substances.

Combined, Arter and Kawaguchi fail to teach or suggest any of these elements. As stated above, Arter does not teach using ferricyanide as an oxidizing agent or a water-soluble coupler.

Kawaguchi teaches a thin-film device for measuring antibody-antigen complex formation and, contrary to the Examiner's position, does not teach the use of maleimide. Rather, this reference teaches the use of long chain hydrocarbon N-substituted maleimides, chemical derivatives of maleimide. The N-substituted maleimides are used to attach antibody (antigen) to the thin-film device, and not to protect the device against interfering substances in samples. Indeed the N-substituted maleimides of Kawaguchi would fail to protect against interferents, as the reactive center of these compounds have antibody (antigen) covalently bound thereto. In sum, Kawaguchi teaches using a compound which is not maleimide and which would be inoperative in the claimed analytical element.

For the reasons put forth above, the analytical element of claims 13, 15 and 16 would not have been *prima facie* obvious under 35 U.S.C. 103 over Arter and Kawaguchi. Alternatively, claims 13, 15 and 16 would not have been obvious under 35 U.S.C. 103 over these references for the reasons stated.

The Examiner also rejected claims 1-7, 9-12, 14, and 17 under 35 U.S.C. 103 as allegedly unpatentable over Hammond in view of either Matsumoto or deCastro and further in view of Batz. Claims 1-7 and 12 have been canceled hereinabove.

In response, applicants respectfully traverse the Examiner's rejection, and maintain that the Examiner has not established a *prima facie* case of obviousness. Claims 9-11, 14, and 17 provide an analytical element comprising, inter alia, a ferricyanide salt as an oxidizing agent, a water-soluble coupler, gelatin, and a buffer to maintain a pH of range of between about 6.5 to 8.5. Together, the references fail to teach or suggest the combination

of these elements. A more detailed discussion of the references follows.

Hammond teaches an aqueous method of determining acetaminophen using an arylacylamidase to catalyze hydrolysis of acetaminophen. The catalysis produces p-aminophenol, which is then converted to a dye via oxidation. The reference teaches that this conversion occurs with sufficient sensitivity and rapidity only at a pH of greater than 9.2 (Fig. 1, page 155). This teaching is also mentioned in the subject specification (page 1, lines 34-36). However, as is stated in the specification, gelatin hardening is accelerated at such alkaline pH. The problems of anticipated gelatin hardening and the anticipated slow oxidation of p-aminophenol at a more acidic pH were unexpectedly overcome in the claimed dry analytical element using ferricyanide salts (page 3, lines 11-26).

Matsumoto teaches a method for condensing aromatic amines with certain aromatic couplers to form dye in solution. Matsumoto fails to teach or suggest the necessity of water-soluble couplers, a critical element of the claimed invention. Moreover, the reference even fails to teach the couplers of the instant claims. The species of couplers which Matsumoto does teach do not even have the properties required in the instant invention (see Table II, pp 15 and 16 of the specification, couplers 6, 7, 8, and 9).

deCastro teaches a method of stabilizing arylacylamidase using phenol derivatives. These derivatives may also serve as coupling agents to produce chromogens upon oxidative condensation with p-aminophenol. deCastro does not teach dry analytical elements comprising gelatin.

Most importantly, deCastro teaches away from using ferricyanide salts as oxidizing agents, as is done in the claimed invention. Specifically, deCastro teaches that such oxidative coupling is catalyzed by Fe III under alkaline conditions (col 2, lines 1-16). deCastro teaches further that Fe III is not desirable and that a "novel catalyst/oxidant" is required, such as periodates (col 2, lines 62 -68, bridging col 3, lines 1-8).

Finally, Batz teaches the use of aniline derivatives as coupling agents for determining oxidizing agents such as hydrogen peroxide or Fe III. Batz teaches the use of 1-(3-sulfopropyl)-1,2,3,4-tetrahydroquinoline. However, Batz fails to teach or suggest dry analytical elements, the use of the disclosed couplers in dry formulations, or the combination of ferricyanide salts with these couplers.

Modification of the assay compositions and methods described by Hammond with the teachings of Matsumoto in light of Batz does not lead to the instant invention. The specification, as mentioned, teaches that the couplers of Matsumoto do not yield the desired performance in dry analytical elements. Batz does not teach or suggest dry analytical elements or the requirement for water-soluble couplers therein. None of these references even suggests dry analytical elements -- let alone dry analytical elements comprising gelatin and, therefore, the unexpected utility of ferricyanide salts.

Additionally, one of ordinary skill in the art would not seek to modify the assays and methods of Hammond to employ ferricyanide salts as oxidizing agents in view of deCastro, because deCastro teaches that such oxidizing agents are undesirable. Even if the teachings of Hammond, deCastro, and Batz were combined, one would not expect to obtain the instant

invention as claimed. Although deCastro mentions elements comprising filter paper, there is no teaching or suggestion that these elements comprise gelatin. Accordingly, no combination of the cited references teaches or suggests all of the elements of the instant invention.

For the reasons put forth above, the analytical element of claims 9-11, 14 and 17 would not have been *prima facie* obvious under 35 U.S.C. 103 over Hammond in view of either Matsumoto or deCastro and further in view of Batz. Alternatively, claims 9-11, 14 and 17 would not have been obvious under 35 U.S.C. 103 over these references for the reasons stated.

The Examiner rejected claims 8, 13, 15, and 16 under 35 U.S.C. 103 as allegedly unpatentable over Hammond in view of either Matsumoto or deCastro and further in view of Batz and further in view of Kawaguchi. Claim 8 has been canceled hereinabove.

In response, applicants respectfully traverse the Examiner's rejection, and maintain that the Examiner has not established a *prima facie* case of obviousness.

Claims 13, 15, and 16 provide an element containing maleimide. As discussed above, Kawaguchi teaches using a compound which is not maleimide and which would be inoperative in the claimed element at removing interferences.

For these reasons, the analytical element of claims 13, 15, and 16 would not have been *prima facie* obvious under 35 U.S.C. 103 over Hammond in view of either Matsumoto or deCastro and further in view of Batz and further in view of Kawaguchi.

Alternatively, claims 13, 15, and 16 would not have been obvious under 35 U.S.C. 103 over these references for the reasons stated.

**Rejection Under 35 U.S.C. 112, Second Paragraph**

The Examiner rejected claims 1-17 under 35 U.S.C. 112, second paragraph, requiring correction of certain informalities. In response to the rejection, applicants have amended the claims to correct these informalities.

In view of the amendments and remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

Respectfully submitted,



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